Responding (or not) to Signals of Potential Clinical Significance in Pragmatic Clinical Trials: Introducing the Ethical Challenge

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Common Data Elements

- Trials are getting larger and collecting greater volumes of clinical data than ever before, often as part of Common Data Elements (CDEs)
- For example, CDEs for pain trials can include data variables and responses related to:
  - pain,
  - pain sequelae,
  - physical functioning,
  - experience with treatment, and
  - other associated behavioral and mental health conditions and risk factors

A challenge

- These data increasingly include information that might signal physical, mental health or behavioral health risks to patient-subjects (e.g., substance use, depression, anxiety, suicidality)
  - Whose responsibility to monitor?
  - What should be monitored and how?
  - Who can and should act/respond?
  - What do patients and other stakeholders desire?

Managing risks in explanatory trials

- Ethical responsibilities for monitoring and responding to signals of health risk during trials have been described and debated
- Several factors noted, e.g.,
  - the nature, magnitude and likelihood of the harm;
  - research participants' vulnerability; and
  - whether the potential harm is directly, indirectly, or not at all associated with the research intervention or interaction with participants
- Ethical obligations are sometimes rooted in one's 'duty of care' and commitment to 'beneficence' in research

Additional complexities with PCTs

- Overlapping roles and responsibilities of clinical and research staff
- Collection of broad sets of CDEs can make data monitoring more challenging
- Various and combined methods for data collection, e.g,, extraction from health records and/or have treating clinicians or patients complete measures
- Trials may operate under waivers of consent

Possible for risk-signaling data to “slip between the cracks”

Implications for the conduct of both research and clinical practice

Factors to consider when addressing ethical obligations

- When trials collect risk-signaling data related to study outcomes, researchers and other stakeholders (e.g., IRBs/sponsors) should:
  - understand and align stakeholder expectations
  - consider characteristics of the trial and study population to inform response
  - define triggers, thresholds, and responsibilities for action
  - identify appropriate response mechanisms and capabilities
  - integrate responses with clinical practices and systems, and
  - address privacy demands

- No single factor more important than another

Ali J, Morain SR, O'Rourke PP, Wilfond B, O'Brien EC, Zigler CK, Staman KL, Weinfurt K, Sugarman J. Responding to signals of mental and behavioral health risk in pragmatic clinical trials: Ethical obligations in a healthcare ecosystem. Contemporary clinical trials. 2022 Jan 5:106651.

Recommendations (Example)

Domain	Recommendations	Additional considerations
Define triggers, thresholds, and responsibilities for action	• Identify *a priori* what thresholds might trigger different types of responses. • Develop an appropriate schedule for ongoing review during the course of the trial to ensure alerts are being triggered as expected and are providing responding parties with adequate information.	Thresholds may vary based on: • the specific context • the information being collected • confidence in the accuracy of the information (e.g., validity of the PRO) • how closely that information is linked with a negative outcome (e.g., suicide) • the overall severity of the potential negative outcome • the expected frequency of the event.

Selected references

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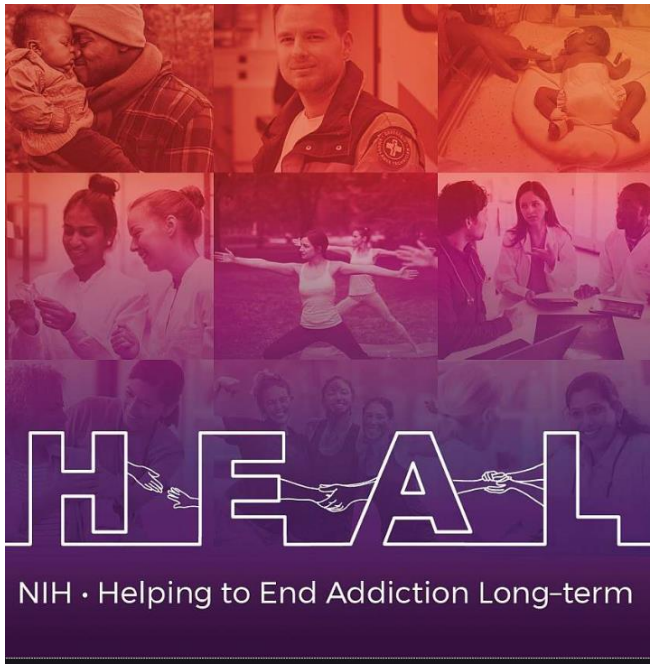


NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

NIH NIAMS

FIBROMYALGIA TENS IN PHYSICAL THERAPY (FM-TIPS)

NIH-FUNDED PRAGMATIC CLINICAL TRIAL

STUDY OVERVIEW

- **Goal**:
  - Demonstrate the feasibility of adding TENS to treatment of patients with FM in a real-world *Physical Therapy* practice setting **and**
  - Determine if addition of TENS to standard *Physical Therapy* for FM reduces pain, increases adherence to PT and allows patients with FM to reach their specific functional goals with less drug use.
- **Hypothesis**
  - Using TENS in a *Physical Therapy* setting is feasible and FM patients using TENS are more likely to reach their therapeutic goals.

TABLE 1. Elements of a Pragmatic Trial	
PRECIS-2 DOMAIN	Description
Eligibility Criteria	Who is selected to participate in the trial? *All individuals with a CLINICIAN DIAGNOSIS of FM and who do not have contraindication to TENS will be eligible to participate.*
Recruitment	How are participants recruited into the trial? *We will recruit participants when they arrive for their regular PT referral visit at a diverse range of PT practices.*
Setting	Where is the trial being done? *The study will be conducted at PT practice sites in the Midwest. The sites will be highly diverse with both small and large private networks with urban and rural locations and will also include University-affiliated practices. These settings are identical to the setting in which the results would be applied.*
Flexibility	How should the intervention be delivered and how will adherence be determined? *This study uses TENS as an adjunct to usual care which will be individualized according to each therapists' usual practice. We will provide information to clinics on the optimal parameters for use of TENS for pain relief. Adherence to PT and to TENS will be determined by EHR and extracted from the device.*
Follow-up	How closely are participants followed? *Each participant will be followed clinically according to the frequency of visits prescribed by their therapist. The study team may contact participants with reminders to complete PRO.*
Primary Outcome	How relevant is it to participants? *The primary outcome for the study is movement evoked pain, one of the primary symptoms of FM and one that interferes with adherence to PT and patient-specific functional goals.*
Primary Analysis	To what extent are all data included? *There is no allowance for non-adherence or practice variability. We will use an intention-to-treat analysis.*

STAKEHOLDERS

- Study Participants
  - Understand that the study is about FM pain and role for TENS
  - No expectation that the treatment is targeting mental health or substance abuse issues
- Clinicians
  - Physical therapists and physical therapist assistants in practice
  - Most without research experience
  - Patients can self-refer in most of the sites
  - Follow professional standards
- Study Team
  - Located at distance from sites
  - Relationship with physical therapists
  - No clinical relationship with patients
  - No relationship with referring providers
- Institutional Review Board
  - Assure a plan is in place to assure participant safety
  - Ensure conformity with institutional policies and protocol
- Data Safety Monitoring Board and Funding Agencies
  - Advisory body to develop that safety plan
  - Responsible for reviewing clinical trial data on an ongoing basis to ensure the safety of study subjects, and validity and integrity of the data

HEAL GRID OF CORE PAIN DOMAINS AND QUESTIONNAIRES

Adult Acute Pain *(Number of total CDE Questions - 39 questions)**

	Pain Intensity	Pain Interference	Physical Functioning / QOL	Sleep	Pain Catastrophizing	Depression	Anxiety	Global Satisfaction with Treatment	Substance Use Screener
Core									
	BPI pain severity	BPI Pain Interference	PROMIS Physical Functioning Short Form 6b	PROMIS Sleep Disturbance 6a + Sleep Duration Question	Pain Catastrophizing Scale – Short Form 6	PHQ-2	GAD-2	PGIC	TAPS 1

Adult Chronic Pain *(Number of total CDE Questions - 30 questions)**

	Pain Intensity	Pain Interference	Physical Functioning / QOL	Sleep	Pain Catastrophizing	Depression	Anxiety	Global Satisfaction with Treatment	Substance Use Screener
Core									
	PEG		PROMIS Physical Functioning Short Form 6b	PROMIS Sleep Disturbance 6a + Sleep Duration Question	Pain Catastrophizing Scale – Short Form 6	PHQ-2	GAD-2	PGIC	TAPS 1

FM-TIPS HEAL CDE

- BPI
- PROMIS PhysFunct
- PROMIS Sleep
- PCS
- PHQ-8
- GAD-7
- TAPS1

PROSPECTIVELY DEFINED ETHICAL CONCERNS

- HEAL instruments could identify actionable clinical issues including serious mental health concerns or substance use disorders
- Depression and anxiety are common in chronic pain (generally) and fibromyalgia (specifically)
- DSMB and study team considered how to manage concerning responses to HEAL questionnaires
  - No plan to do real-time monitoring of questionnaires
  - Actionable threshold unclear
- Mitigating factors
  - Previous RCT in a similar population with ~300 participants had no serious adverse events related to mental health or substance use
  - Physical therapists are trained to discuss and manage mental health issues

DECISION

- Physical therapists at all enrolling sites had procedures in place to identify mental health and substance use concerns and communicate with referring providers. Physical therapists are mandatory reporters of potential harm to self or others.

- Added language to the informed consent document:

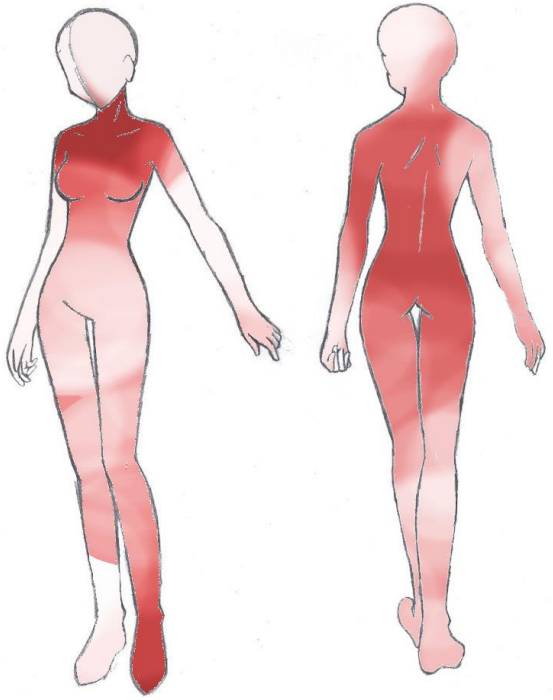
> **WILL I BE NOTIFIED IF MY DATA RESULT IN AN UNEXPECTED FINDING?**
>
> The results from the data we collect in this research study are not the same as what you would receive as part of your routine health care. The data results will not be reviewed by a physician who normally reads such results. Due to this, you will not be informed of any unexpected findings. The results of your data will not be placed in your medical record with your primary care physician or otherwise. If you believe you are having symptoms that may require care, you should contact your primary care physician.

- Study team to conduct periodic (monthly) monitoring of data to identify any signals but otherwise to rely on clinicians to manage issues as is standard in PT practice

EMERGENT ETHICAL ISSUE

- Fibromyalgia is an infrequent reason for referral to PT though a very common comorbidity of neck/back pain at ~30%
- As a part of study procedures, it is requested that all patients whose primary reason for PT referral are screened
- Most frequent exclusion was lack of a clinician diagnosis of fibromyalgia
- Fibromyalgia can be diagnosed based on responses to a questionnaire
  - American College of Rheumatology 2016 criteria
- Clinical diagnosis and criteria-based diagnosis are not perfectly aligned

FIBROMYALGIA IS ASSOCIATED WITH WIDESPREAD PAIN, CO-MORBID SYMPTOMS, AND CENTRAL SENSITIVITY



Fibromyalgia Diagnostic Criteria 2016

1. Generalized pain
2. >3 months
3. Fibromyalgia Severity Scale
   a. Widespread Pain Index
   b. Symptom Severity Scale

Mansfield 2016, Wolfe 2016

EMERGENT ETHICAL ISSUE

- What would be the implications of including the ACR Criteria to screening to increase eligibility?
  - Participants
    - Might not know anything about fibromyalgia
    - Not the reason for the referral to PT
    - May or may not be happy about being diagnosed with fibromyalgia
    - Might be a stigmatizing diagnosis
  - Clinicians
    - Making medical diagnoses is not within scope of practice for physical therapy clinicians, though they often collect information that might guide treatment
    - Unclear how to relate the information back to the referring provider, if the patient was referred, who may have concerns about this diagnosis
  - Study Team
    - No clinical relationship with participants
    - No mechanism in place to educate patients
    - No mechanism in place to interact with referring provider (if there was a referral)
  - DSMB/Funding agencies
    - Receptive to implementation

DECISION

- Discussion with NIH Pragmatic Trials Collaboratory Ethics and Regulatory Core
- Study team made the decision that making a new diagnosis unknown to the participant was beyond the scope of a pragmatic trial in a PT setting
- Should FM-TIPS demonstrate that implementing TENS in PT improved outcomes and was feasible, clinicians would have a rationale for determining if patients met fibromyalgia criteria thus would benefit from treatment

Responding (or not) to Signals of Potential Clinical Significance in Pragmatic Clinical Trials: Thoughts from the IRB (*It depends…)*

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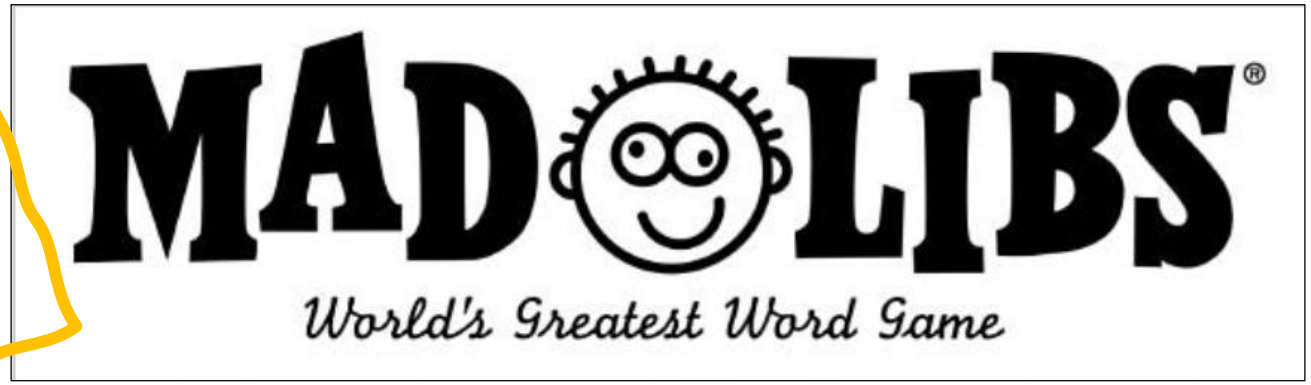
IRB



Does the _____ have an obligation
noun

to the _____ to share _____ clinically
noun adverb

relevant information?

Does the _____ have an obligation

investigator
provider
care delivery system

noun

to the _____ to share _____ clinically

participant
subject
patient
provider
care delivery system

noun

potentially
actually

adverb

relevant information?

Did the IRB already work through this?

Yes, we thought of that!

Move forward or reconsider approved plan.

***!@#$*, we didn't think of that!**

Now what?

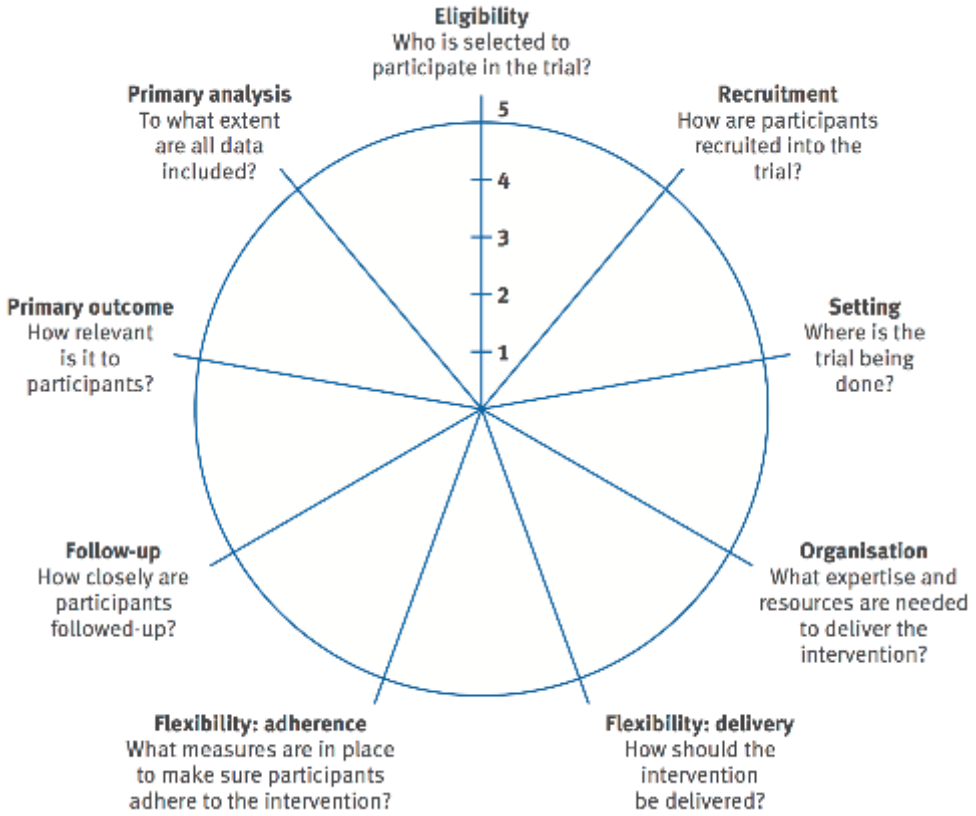
- Is it actionable?
- If yes, who owns the responsibility to inform?

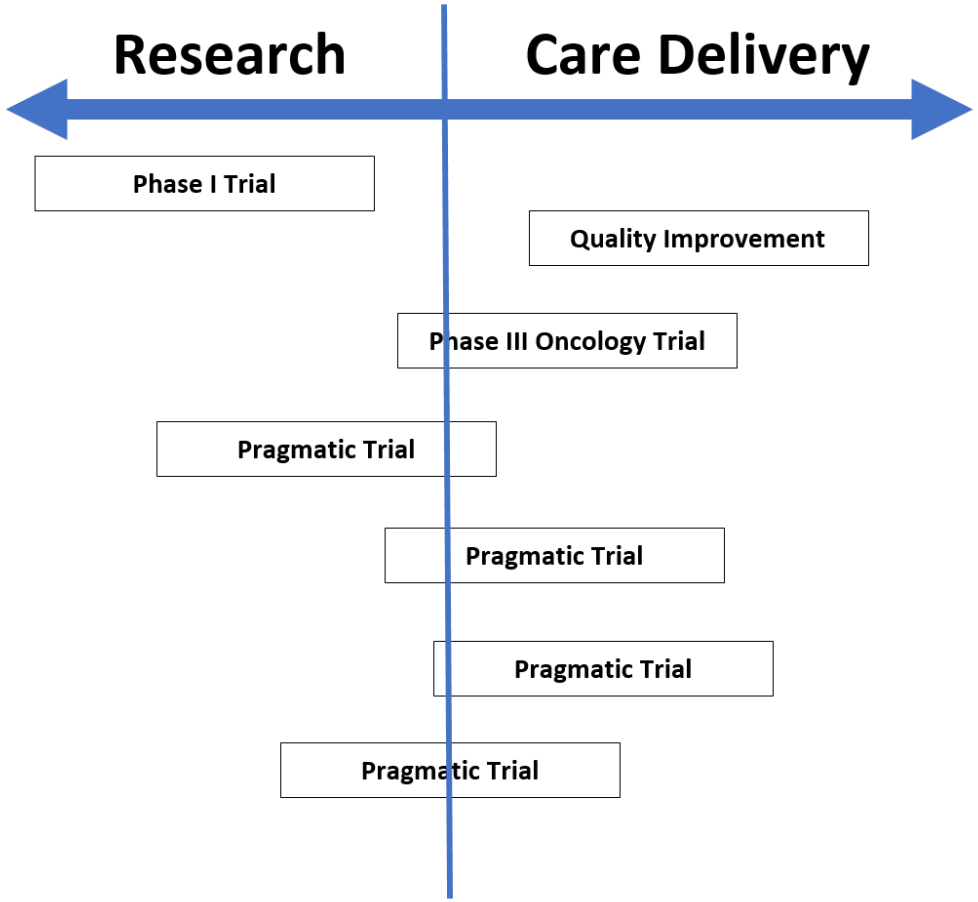
…_*potentially* / *actually*_ clinically relevant information?…

adverb

- Is the information really actionable/relevant? For all participants or just some?
- Quality of the data?
- Consultation with researchers, IRB members/chair, care delivery, outside experts
- Do we know anything at all about whether the patients/participants/ subjects might want the information?
- Do we know anything at all about whether the care delivery system or clinic will see this as important/relevant/actionable given their standard of care?

…the *investigator / provider / care delivery system* (noun) have an obligation to the *participant / subject / patient / provider / care delivery system* (noun) …





The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel.

…the *investigator / provider / care delivery system* (*noun*) have an obligation to the *participant / subject / patient / provider / care delivery system* (*noun*) …

Researchers

- Regulatory requirements
- Ethical considerations
- Institutional policies or guidelines

Provider/Care Delivery

- Regulatory requirements
- Legal requirements?
- Ethical considerations
- Provider/clinic/care delivery policies or guidelines

Subject/Participant/Patient

- Self interest?

Does the _____ have an obligation
investigator
noun

to the _____ to share _____ clinically
participant
noun
potentially
adverb

relevant information?

Does the *care delivery system* (noun) have an obligation to the *patient* (noun) to share *potentially* (adverb) clinically relevant information?

…and _____ has the responsibility to follow-up

noun

Researchers

- Regulatory requirements
- Ethical considerations
- Institutional policies or guidelines

Provider/Care Delivery

- Regulatory requirements
- Legal requirements?
- Ethical considerations
- Provider/clinic/care delivery policies or guidelines

Subject/Participant/Patient

- Self interest?